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Diagnosis, treatment and long-term outcome of solitary fibrous tumours of the pleura

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Russi, Erich W ; Weder, Walter

Abstract: Objective: Solitary fibrous tumours of the pleura (SFTP) are rare and can histologically be differentiated into benign and malignant forms. The aim of this study is to present new cases, and discuss up-to-date preoperative examinations, the role of video-assisted thoracic surgery and long-term outcome. Methods: Between 1993 and 2006, 27 SFTPs were diagnosed (14 females, mean age \pm SD, 62.3 \pm 9.6 years) at our institution. Medical records were reviewed, and follow-up was obtained by repeated examinations or contact with general practitioners. Results: SFTPs were associated with symptoms in 63% of all cases. In the six patients in which positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) was performed preoperatively, malignant lesions were all found to be positive. Complete resection was achieved by video-assisted thoracic surgery in 15 and anterolateral thoracotomy in 12 patients. Mean hospital stay was shorter for patients operated by video-assisted thoracic surgery compared to thoracotomy, 4.5 (range 3-6) versus 7.5 (range 4-25) days, respectively (p 0.01). Histology revealed 17 benign and 10 malignant SFTP. Mean \pm SD tumour diameter of malignant SFTPs was larger than in benign forms, 11.9 \pm 7.1 versus 6.1 \pm 3.5cm, respectively (p 0.01). Tumour recurrence was recognised in four patients with malignant SFTPs at a median time interval after surgery of 38 (range 6-122) months, two late deaths occurred resulting from tumour recurrences. Conclusions: SFTPs can be treated minimally invasively by video-assisted thoracic surgery with short hospital stay. Large SFTPs with increased FDG-uptake have a high likelihood for malignancy. Long-term follow-up is mandatory in malignant SFTPs because of late recurrences associated with death

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Diagnosis, treatment and long-term outcome of solitary fibrous tumours of the pleura

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Abstract

Objective: Solitary fibrous tumours of the pleura (SFTP) are rare and can histologically be differentiated into benign and malignant forms. The aim of this study is to present new cases, and discuss up-to-date preoperative examinations, the role of video-assisted thoracic surgery and long-term outcome. **Methods:** Between 1993 and 2006, 27 SFTPs were diagnosed (14 females, mean age \pm SD, 62.3 ± 9.6 years) at our institution. Medical records were reviewed, and follow-up was obtained by repeated examinations or contact with general practitioners. **Results:** SFTPs were associated with symptoms in 63% of all cases. In the six patients in which positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) was performed preoperatively, malignant lesions were all found to be positive. Complete resection was achieved by video-assisted thoracic surgery in 15 and anterolateral thoracotomy in 12 patients. Mean hospital stay was shorter for patients operated by video-assisted thoracic surgery compared to thoracotomy, 4.5 (range 3–6) versus 7.5 (range 4–25) days, respectively ($p < 0.01$). Histology revealed 17 benign and 10 malignant SFTP. Mean \pm SD tumour diameter of malignant SFTPs was larger than in benign forms, 11.9 ± 7.1 versus 6.1 ± 3.5 cm, respectively ($p < 0.01$). Tumour recurrence was recognised in four patients with malignant SFTPs at a median time interval after surgery of 38 (range 6–122) months, two late deaths occurred resulting from tumour recurrences. **Conclusions:** SFTPs can be treated minimally invasively by video-assisted thoracic surgery with short hospital stay. Large SFTPs with increased FDG-uptake have a high likelihood for malignancy. Long-term follow-up is mandatory in malignant SFTPs because of late recurrences associated with death.

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Keywords: Pleura; Solitary fibrous tumour; Video-assisted thoracoscopic surgery; Positron emission tomography

1. Introduction

Solitary fibrous tumours of the pleura (SFTP) are rare neoplasms, and approximately 800 cases have been reported in the literature so far [1]. It has been demonstrated by immunohistochemical staining and electron microscopy that these tumours are of mesenchymal origin [2,3]. A majority are benign and characteristically grow as well-circumscribed, pedunculated lesions attached to the visceral and less commonly to the parietal pleura [4]. Treatment of choice is surgical excision and recurrence of these tumours is scarce if resection is histologically complete [1,5]. However, features of malignancy, characterised by poor circumscription, infiltration of adjacent structures, high mitotic activity

and nuclear pleomorphism, are found in 7–60% of SFTPs [4,6,7]. Additionally, some benign SFTP may transform into the malignant form even after several years [8]. Outcome of malignant SFTPs is less favourable, and deaths related to local invasion, recurrence, or metastases are reported in the literature [4]. Therefore, there is a need to outline parameters that characterise the underestimated malignant variant and to better understand its biological behaviour.

A preoperative diagnosis of SFTP by radiological imaging can be difficult and a reliable differentiation between malignant and benign forms is often impossible with computed tomography scanning (CT) or magnetic resonance imaging (MRI). Benign and malignant SFTPs usually appear as well circumscribed, homogeneous, and at times lobulated masses with the density of soft tissue in CT scans. CT heterogeneity, large tumour diameter, and pleural effusion are more likely to be found in malignant forms, but may also be observed in benign variants [1,4,9,10]. Furthermore, diagnostic accuracy of CT-guided aspiration biopsy is

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unsatisfactory [6,8,11]. To date there is very little data available from positron emission tomography (PET) with [18 fluorine]fluorodeoxyglucose (FDG) performed in patients with these tumours [12,13]. FDG-PET could possibly predict or rule out malignancy in SFTP preoperatively and reveal metastatic recurrence, an event rarely observed in these tumours [4].

Recently, video-assisted thoracoscopic surgery (VATS) has been introduced for the treatment of SFTP which is thought to result in shorter hospital stay and less postoperative morbidity, but comparative data between VATS and thoracotomy are scant [5]. In order to define the clinical and radiological pattern of benign and malignant SFTP more accurately and evaluate the role of VATS as a less invasive treatment option we summarise our experience in the management of SFTP.

2. Materials and methods

From January 1993 to March 2006, 27 SFTPs were diagnosed in 27 patients (14 females, mean age \pm SD, 62.3 ± 9.6 years) at our institution. The medical records were reviewed, and follow-up was obtained by repeated examinations of patients or contact with the primary care physician. No history of exposure to asbestos was recorded in any of the patients.

All patients underwent chest X-ray and computer tomography (CT) of the chest preoperatively. Whole body FDG-PET was performed in six patients. FDG uptake was qualitatively assessed, positivity and likelihood of malignancy was defined as focally increased FDG uptake in comparison with the background not related to physiologic processes, combined with a tumour diameter >10 cm or inhomogeneous FDG uptake.

The diagnosis of SFTP was confirmed by typical histomorphologic findings of a solid spindle cell component, and a diffuse sclerosing component combined with matching immunohistochemical staining (positive for vimentin and/or CD34, negative for keratin and/or S-100 protein). SFTPs were classified as benign or malignant according to the histologic criteria published previously [4]. Malignancy was assumed if one or more of the following criteria were met: (1) ≥ 4 mitotic figures per 10 high-power fields (HPF), (2) presence of necrosis or haemorrhage, (3) pleomorphism based on nuclear size, nuclear crowding and overlapping, and the presence of nuclear atypia.

Student's *t*-tests for normally distributed, and Mann–Whitney *U*-tests for not normally distributed data were performed for comparisons between groups. For comparison of frequencies χ -square test of independence or a Fisher's exact test when any of the expected tumour features were fewer than five was used. Statistical significance was assumed at a probability of $p < 0.05$.

3. Results

3.1. Clinical presentation

SFTPs were associated with symptoms in 17 patients (63%), whereas 37% of our patients were asymptomatic.

Table 1
Clinical presentation

Finding	Number of patients	% of total
Asymptomatic	10	37
Symptomatic	17	63
Cough	7	25.9
Thoracic pain	7	25.9
Dyspnoea	3	11.1
Weight loss	2	7.4
Pneumonia	2	7.4
Clubbing	2	7.4
Hypoglycaemia	1	3.7

Cough and thoracic pain were the primary symptoms occurring each in a quarter of all patients. Symptomatic hypoglycaemia was found in only one patient (3.7%).

Twelve patients (44.4%, four females) were smokers or ex-smokers (mean pack years \pm SD, 24.6 ± 16.6 years). Further data on clinical presentation are given in Table 1.

3.2. Preoperative studies

In all patients, standard chest X-ray and CT revealed a pleural tumour. The origin of the tumour was determined in the left hemithorax in 16 patients (59.3%), whereas the right hemithorax was involved in 40.7%. SFTPs were slightly more often found in the lower (55.6%) than in the upper lobe area (40.7%). In one case (3.7%) the lobe of origin could not be determined. Pleural effusion was found in one patient (3.7%) only.

Tumours appeared inhomogeneous on CT in three patients with malignant SFTP and in two patients with benign SFTP ($p = \text{ns}$). Tumour necrosis in histology was only found in patients with malignant lesions. Tumour invasion into the chest wall was radiologically suspected in one patient with malignant SFTP, which was subsequently confirmed during surgery and by histology. Calcification of the tumour was detected by CT in one patient with malignant and in two patients with benign SFTP.

In six patients, three with malignant and three with benign SFTPs, an integrate ^{18}F -fluorodeoxyglucose PET-CT was performed preoperatively. PET-CT was positive in three patients who had a histologically proven malignant SFTP, whereas criteria for positivity were not met in patients with benign SFTP. No signs of lymph node or distant metastases were found in the three cases of malignant SFTPs.

Preoperative CT-guided transcutaneous aspiration biopsy was performed in five patients (18.5%) leading to the correct histologic diagnosis in two cases. A typical example of a CT scan from a patient with SFTP is shown in Fig. 1.

In seven patients (25.9%) the tumour was present on radiological imaging performed more than 6 months previously (median 42 months, range 7–156 months) and had been judged as a benign lesion. Patients were finally referred for surgery because of an increase in size or emerging clinical symptoms. In three of these seven patients the SFTPs were histologically found to be malignant.

Lung function testing revealed a moderate restrictive ventilatory defect in one patient caused by a large SFTP ($23 \text{ cm} \times 21 \text{ cm} \times 7 \text{ cm}$). An obstructive pattern was determined in three other patients with COPD (GOLD-stage I–II)

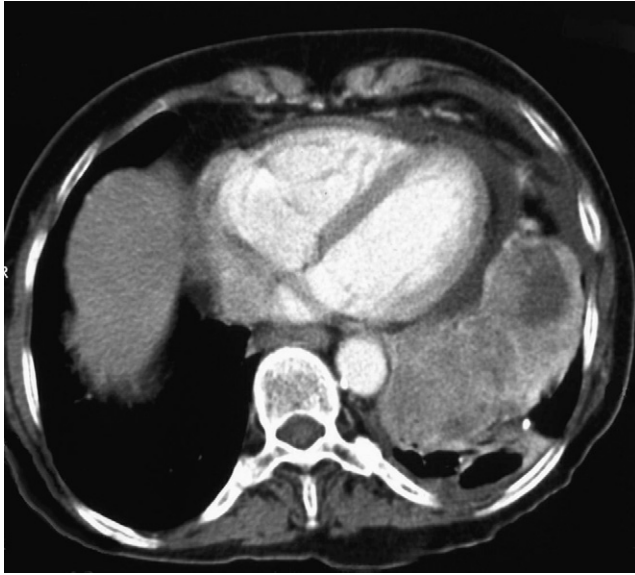


Fig. 1. Computed tomographic scan showing a left-sided broad based solitary fibrous tumour of the pleura with a characteristic pedicle (histological examination revealed a benign variant).

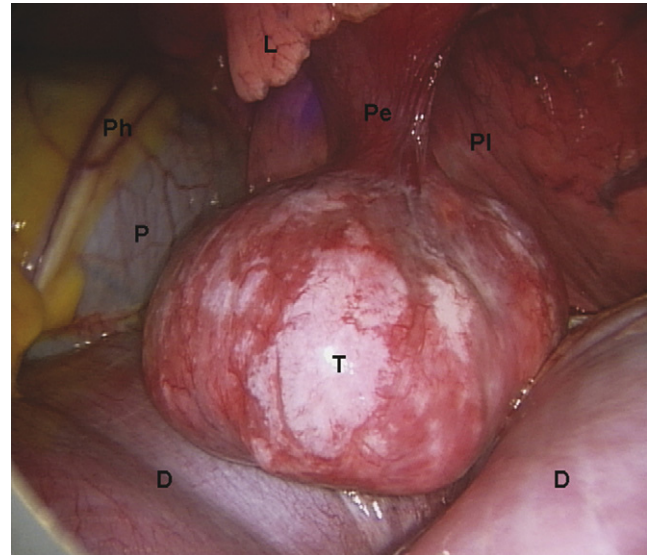


Fig. 2. Intraoperative photograph showing the characteristic pedicle (Pe) of a large solitary fibrous tumour of the pleura. L: lung; Ph: phrenic nerve; P: pericard; T: tumour; D: diaphragm; Pl: pleura.

due to smoking. Bronchoscopy was performed in eight patients and provided no relevant additional information.

3.3. Treatment

Complete resection was achieved in all 27 patients. In all patients a single lesion was found at surgical exploration. Tumours originated from the visceral pleura in 88.8%, a pedicle was present in 59.3% of the cases (e.g. Fig. 2). In three cases (11.1%) the lesions arose from the parietal pleura (two of them were malignant). Macroscopically a tumour-capsule was found in 74.1%.

In 85.2% of the cases removal of the neoplasm was either accomplished by dividing the pedicle close to or with a small rim of lung parenchyma (tumours arising from the visceral pleura) or by a pleural excision (tumours originating from the parietal pleura). Lobectomy was necessary in one and pneumonectomy in three patients due to extensive adhesions and intraparenchymal extension of the tumour.

Anterolateral thoracotomy was performed in 12 patients (44.4%, in 1 patient anterolateral thoracotomy was combined with upper median sternotomy because of very large tumour size), whereas surgical resection was accomplished by VATS in 15 patients (55.6%). Mean hospital stay was significantly shorter for patients operated by VATS than by thoracotomy, 4.5 (range 3–6) versus 7.5 (range 4–25) days, respectively ($p < 0.01$). Duration of hospitalisation was longer in patients with malignant SFTP (median 8, range 3–25 days) compared to patients with benign SFTP (median 5, range 3–7 days, $p < 0.05$).

Major perioperative complications occurred in one patient in the VATS group (bleeding) and in three patients undergoing thoracotomy (one patient with sepsis, one patient with pneumopleural leakage, one patient with atrial fibrillation, liver and renal failure). There was no perioperative mortality reported in either group.

As expected, mean tumour diameter was larger in the thoracotomy group, 12.4 cm (range 3.0–23 cm) versus 4.9 cm (range 2.0–9.5 cm) in the VATS group ($p < 0.01$).

3.4. Pathology

Maximal tumour diameter ranged from 2 cm in the smallest to 23 cm in the largest tumour with an average of 8.2 cm. Mean tumour volume was 460 cm³ (range 1.6–4301 cm³).

Histological examinations revealed 17 benign (63%) and 10 malignant (37%) SFTPs. All malignant tumours showed more than 4 mitoses per 10 HPFs. Malignant SFTPs were bigger and occurred more often in men than in women. Malignant SFTPs were equally distributed between smokers and non-smokers. Recurrence of the tumour was only recognised in malignant forms.

Immunohistochemical analysis was performed in 23 cases. All tumours were positive for CD34 and/or vimentin, while none showed a positive reaction to antikeratin antibodies.

Comparative data between malignant and benign SFTPs are given in Table 2. A typical example of histological photomicrographs from a SFTP is shown in Fig. 3.

3.5. Follow-up

Median follow-up time for all patients was 54 (range 6–157) months. Local recurrence of the tumour was recognised in the CT scan of four patients (14.8%) at a median time interval after surgery of 38.5 (range 6–122) months. All relapses occurred in patients with malignant SFTPs, and all of them were reoperated and the diagnosis of a relapse was histologically confirmed. In total three deaths occurred: one patient had a total of three local recurrences and eventually died of distant metastases, one patient died of local recurrence of the tumour, and one patient died of an illness

Table 2
Comparison of malignant and benign SFTPs

	Malignant (n = 10)	Benign (n = 17)	p
Age (years)	66.5 ± 6.8	59.9 ± 10.6	0.09
Women (%)	30	64.7	0.60
Men (%)	70	35.3	0.007
Smokers (%)	40	47.1	0.52
Symptomatic (%)	80	52.9	0.16
Tumour diameter (cm)	11.9 ± 7.1	6.1 ± 3.5	0.009
Tumour volume (cm ³)	1218 ± 1821	147 ± 276	0.02
Tumour recurrence (%)	40	0	0.005

Values are expressed as means ± standard deviation (where applicable).
Values in bold are statistically significant.

unrelated to the SFTP. Cumulative survival after operation is illustrated in Fig. 4.

4. Discussion

Solitary fibrous tumours of the pleura (SFTP) are rare and their clinical characteristics are not well known. There are only a few studies including an appropriate number of malignant SFTPs and reporting adequate follow-up [1,11,14,15]. Because some of these tumours are asymptomatic and do not show conventional radiological signs of

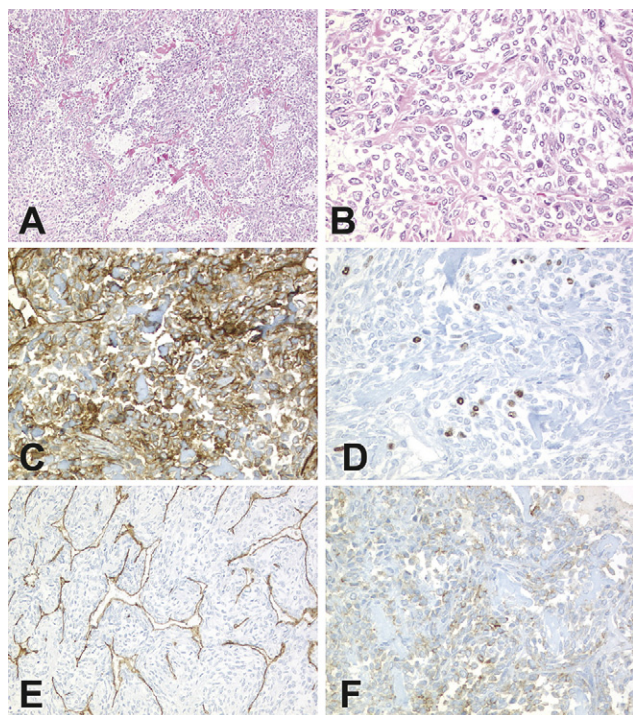


Fig. 3. Photomicrographs of a solitary fibrous tumour of the pleura. The low power magnification haematoxylin-eosin stain (A) shows a high cellular solitary fibrous tumour with characteristic ropey collagen bundles. Higher power magnification haematoxylin-eosin stain (B) demonstrating variable cytological atypia and pleomorphism with occasional mitoses and apoptotic cells. Immunohistochemical staining is strongly positive for CD34 (C). A variable proliferative activity can be detected in a MIB-1/Ki-67 staining (D). Staining for CD31 (E) highlights the characteristic staghorn vascular pattern. Immunohistochemical stainings for CD99 are variably positive in SFTPs (F). Original magnifications 10× (A), 80× (B, C, D, F) and 40× (E).

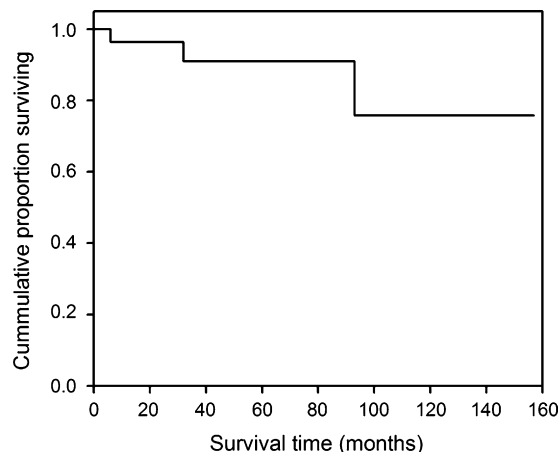


Fig. 4. Kaplan–Meier curve showing the cumulative survival probability in patients with SFTPs following operation.

malignancy, referral for surgery is sometimes delayed [11]. Furthermore, the diagnostic value of CT-guided aspiration biopsy has been shown to be poor and may not be helpful in making a decision about the need for surgery [6,7,11]. In our series, surgery was delayed in seven (26%) patients (median 42, range 7–156 months) which is similar to previously reported data [11]. In three of these seven patients the SFTPs were histologically found to be malignant, which emphasises the need for early diagnosis and treatment even in asymptomatic cases. There are no specific symptoms that allow differentiation between benign and malignant forms of SFTPs. In contrast to an earlier report, we did not find significantly more symptomatic patients in the malignant group than in the benign group [11]. Interestingly, malignant tumours occurred more often in men compared to women in our study, whereas England et al. [4] found malignant tumours evenly distributed between genders. The size and volume of malignant tumours were greater than in benign SFTPs. Although data from previous series are inconsistent, most authors showed that a larger tumour size is associated with a higher risk of malignancy and local recurrence [1,4,11].

A preoperative diagnosis of SFTP based on radiological imaging can be difficult and a differentiation between malignant and benign forms is often impossible by CT or MRI. In our series inhomogeneous appearance and calcification of the tumour did not discriminate between malignant and benign SFTP, and CT-guided biopsy of the tumour established the correct diagnosis in only two cases out of five which is in accordance with previously published studies [11]. Most authors feel that diagnostic accuracy of CT-guided aspiration biopsy in SFTPs is unsatisfactory [6,8,11]. In our opinion CT-guided biopsy may be helpful in cases where diagnosis of SFTP is uncertain. In an attempt to improve diagnostic accuracy, we retrospectively looked at FDG-PET-scans, and found PET positivity in all patients with malignant SFTPs. To our knowledge there are only a few case reports on FDG-PET in SFTP in the literature. Robinson [12] reported no FDG uptake in two benign SFTPs, and Cortes et al. [13] found FDG-PET negativity in three benign lesions. Because the small number of patients limits our findings and the available information in the literature, prospective studies including a

higher number of patients are needed to further evaluate the accuracy of FDG-PET in differentiating malignant from benign SFTP and to define its role in clinical practice. We believe all patients with SFTPs should undergo surgery without delay, as SFTPs can progress in size causing symptoms and may transform to a malignant tumour, therefore the value of preoperative FDG-PET would be limited to exclusion of tumour metastasis, an event rarely observed in SFTPs [4]. However, some centres apply a strategy of watchful waiting in asymptomatic SFTP and operations may be delayed in countries with long waiting lists. In this setting, an FDG-PET positive SFTP could be considered malignant and should be operated without delay. Furthermore, FDG-PET might be suitable to detect metastases after surgery in patients with malignant SFTP.

We observed a malignant histology in 37% of cases on the basis of criteria suggested by England et al. [4]. The same criteria have been used in recently published studies and they are accepted by the American registry of pathology [1,6,11,16]. The percentage of malignant tumours is similar to that found in other series (e.g. 37% in the study of Magdeleinat et al. [11], 36% in the study of England et al. [4]), but there is a considerable variability ranging from 7 to 60% reported in other studies [5–7]. A likely explanation for the variability might be the difficulty in establishing the criteria for malignancy in large tumours due to heterogeneity of the lesion.

Recently VATS has been reported to be a promising surgical approach for resection of SFTPs resulting in less invasive surgery and therefore minimising postoperative morbidity [5]. Other advantages of VATS are better cosmetic results and in theory less costs because of shorter hospital stays. We found a significantly shorter hospital stay (4.5 days) in patients operated by VATS compared to patients operated by anterolateral thoracotomy (7.5 days). There was a tendency towards fewer postoperative complications occurring in the VATS group (6.7%) in comparison with thoracotomy (25%). Takahama et al. [5] reported a mean duration of hospital stay of 8.6 days in their series of 13 patients including 9 patients operated by VATS; further comparative data between thoracotomy and VATS in SFTPs are lacking. Of note, very large lesions (e.g. >10 cm diameter) and tumours with radiological signs of invasion into the chest wall or intrathoracic organs are not suitable for VATS, and tumour diameter was significantly larger in the thoracotomy group in our study. Furthermore, the extent of resection possibly influences postoperative morbidity and the length of hospital stay, although the differences between VATS and thoracotomy found in our series could not be entirely explained by the different extent of resection.

Local recurrences of SFTPs after complete surgical resection are not uncommon in malignant forms, but are exceptionally rare in benign lesions [1,4]. If recurrence does occur in benign lesions, this may be due to incomplete resection, unrecognised malignancy or growth of an unrelated second SFTP, which has been described previously [4]. We observed recurrence of the tumour during follow-up in 4 out of 10 patients with malignant SFTPs, although some authors report less recurrences [11,17], and in none with benign SFTPs, which is in accordance with other series [4,7]. A possible explanation for these differences could be

different radiological methods used at follow-up. It must be stressed that the minimal-invasive approach by VATS should not compromise an oncologically sound operation, and therefore the type of operation (VATS vs thoracotomy) should not influence tumour recurrence.

De Perrot et al. [1] suggested a follow-up plan after resection of malignant SFTPs with half-yearly radiologic controls by CT in the first 2 years and yearly thereafter. Especially in malignant lesions a long-term follow-up is mandatory because of possible late recurrences, which can be locally aggressive, and lead to death through local invasion and compression, which occurred in two of our patients. In case of recurrence, surgical resection is the treatment of choice with a good chance for complete cure [1]. There are only a few cases described in the literature concerning adjuvant radiotherapy or chemotherapy in malignant SFTPs and their role needs to be established [11].

In conclusion, we found that large SFTPs with increased FDG-uptake have a high likelihood for malignancy, but the role of FDG-PET in clinical practice has to be further defined. VATS is associated with a short hospital stay and minor postoperative morbidity, and is therefore our preferred surgical approach for resection of SFTPs smaller than 10 cm. Long-term follow-up is mandatory in malignant SFTPs because of late recurrences associated with death.

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